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(21) International Application Number: PCT/US96/08105 (22) International Filing Date: 30 May 1996 (30.05.96) (30) Priority Data: 08/481,549          7 June 1995 (07.06.95)          US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BURKÖTH, Terry, L. [US/US]; 711 Torrey Court, Palo Alto, CA 94303 (US). TASKOVICH, Lina, T. [EC/US]; 751 Gailen Avenue, Palo Alto, CA 94303 (US). CRISOLOGO, Nieves, Marzan [US/US]; 787 Madrone Avenue, Sunnyvale, CA 94086 (US). BESTE, Russell [US/US]; 381 Farley Street, Mountain View, CA 94043 (US). HAMLIN, Richard, D. [US/US]; 7471 Braidburn Avenue, Newark, CA 94560 (US). GALE, Robert, M. [US/US]; 1276 Russel Avenue, Los Altos, CA 94024 (US). LEE, Eun, Soo [US/US]; 108 Danbury Lane, Redwood City, CA 94061 (US). YUM, Su, Il [US/US]; 1021 Runnymead Court, Los Altos, CA 94024 (US).		(74) Agents: RAFA, Michael, J. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

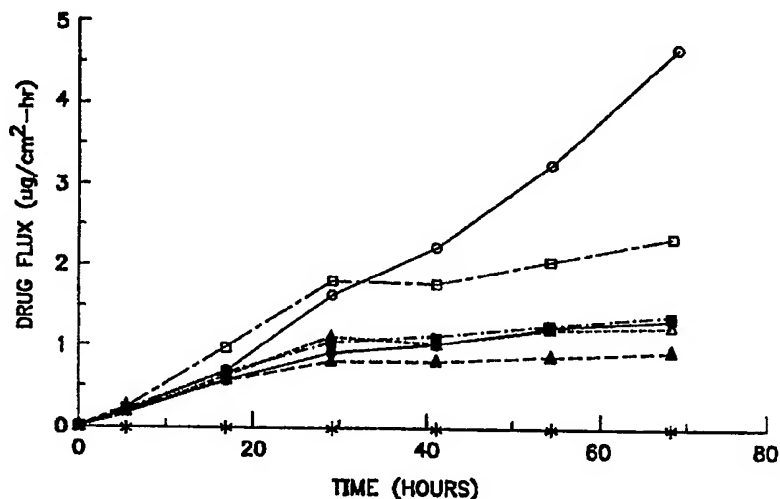
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(54) Title: SKIN PERMEATION ENHANCER COMPOSITIONS COMPRISING GLYCEROL MONOLAURATE AND LAURYL ACETATE

## (57) Abstract

Compositions, devices, and methods for transdermal administration of an active agent are disclosed using a novel dual permeation enhancer mixture comprising lauryl acetate and a monoglyceride, preferably glycerol monolaurate. The dual permeation enhancer mixture comprising lauryl acetate is a potent permeation enhancer and provides stable systems which are more readily characterized.



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1                    **SKIN PERMEATION ENHANCER COMPOSITIONS**  
2                    **COMPRISING GLYCEROL MONOLAURATE AND LAURYL ACETATE**  
3

4                    **RELATED APPLICATIONS**  
5

6                    This application is a continuation-in-part of Ser. No. 481,549, filed  
7                    June 7, 1995, assigned to ALZA Corporation, for which the benefit of the  
8                    earlier filing date is claimed.  
9

10                   **TECHNICAL FIELD**  
11

12                   This invention relates to the transdermal delivery of agents or other  
13                   biologically active agents and more particularly to methods and compositions  
14                   for enhancing the percutaneous absorption of agents or other agents when  
15                   incorporated in transdermal agent delivery systems or devices. More  
16                   particularly, this invention relates to the transdermal delivery of agents  
17                   utilizing a novel dual permeation enhancer comprising glycerol monolaurate  
18                   and lauryl acetate.  
19

20                   **DESCRIPTION OF TERMS**  
21

22                   As used herein, the term "transdermal" means percutaneous delivery  
23                   of an agent through skin or mucosal tissue into the circulation by topical  
24                   application.

25                   As used herein, the term "therapeutically effective" amount or rate  
26                   refers to the amount or rate of agent or active agent needed to achieve a  
27                   desired therapeutic result.

As used herein, the phrase "predetermined area of skin" refers to a defined area of intact unbroken skin or mucosal tissue. That area is usually in the range of about 5 cm<sup>2</sup> to about 100 cm<sup>2</sup>.

As used herein, the term "monoglyceride" refers to a monoglyceride of a fatty acid or a mixture of monoglycerides of fatty acids, or mixtures thereof with other materials in which the monoglyceride component comprises at least 50% by weight, and includes, for example, glycerol monolaurate, glycerol monooleate, and glycerol monolinoleate.

9           As used herein, "glycerol monolaurate" refers to glycerol monolaurate  
10   itself or a mixture of glycerides wherein glycerol monolaurate is present in the  
11   greatest amount.

As used herein, "glycerol monooleate" refers to glycerol monooleate itself or a mixture of glycerides wherein glycerol monooleate is present in the greatest amount.

As used herein, "glycerol monolinoleate" refers to glycerol monolinoleate itself or a mixture of glycerides wherein glycerol monolinoleate is present in the greatest amount.

18 As used herein, the phrase "water absorbing polymer" refers to a  
19 hydrophilic polymer being able to absorb water and includes, but is not limited  
20 to, polyvinyl pyrrolidones, polyvinyl alcohol, and polyaminoacrylates.

22 BACKGROUND ART

The transdermal route of parenteral delivery of drugs provides many advantages, and transdermal systems for delivering a wide variety of drugs or other beneficial agents are described in U.S. Patent Nos. 3,598,122; 3,598,123; 3,731,683; 3,797,494; 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,559,222; 4,568,343; 4,573,999; 4,588,580; 4,645,502;

1 4,704,282; 4,816,258; 4,849,226; 4,908,027; 4,943,435; and 5,004,610, for  
2 example,  
3 all of which are incorporated herein by reference. In many cases, agents  
4 which would appear to be ideal candidates for transdermal delivery are found  
5 to have such low permeability through intact skin that they cannot be  
6 delivered in therapeutically effective amounts from reasonably sized devices.

7 In an effort to increase skin permeability so that agents can be  
8 delivered in therapeutically effective amounts at therapeutically effective  
9 rates, it has been proposed to pretreat the skin with various chemicals  
10 or to concurrently deliver the agent in the presence of a permeation  
11 enhancer. Various materials have been suggested for this, as described  
12 in U.S. Patent Nos. 3,472,931; 3,527,864; 3,896,238; 3,903,256; 3,952,099;  
13 4,046,886; 4,130,643; 4,130,667; 4,299,826; 4,335,115; 4,343,798;  
14 4,379,454; 4,405,616; 4,746,515; 4,788,062; 4,820,720; 4,863,738;  
15 4,863,970; and 5,378,730; British Pat. No. 1,011,949; and Idson,  
16 "Percutaneous Absorption," J. Pharm. Sci. (1975) 64:901-924.

17 To be considered useful, a permeation enhancer should have the  
18 ability to enhance the permeability of the skin for at least one and preferably a  
19 significant number of agents. More importantly, it should be able to enhance  
20 the skin permeability such that the agent delivery rate from a reasonably  
21 sized system (preferably 5-50cm<sup>2</sup>) is at therapeutic levels. Additionally, the  
22 enhancer when applied to the skin surface, should be non-toxic, non-irritating  
23 on prolonged exposure and under occlusion, and non-sensitizing on repeated  
24 exposure. Preferably, it should be odorless and capable of delivering agents  
25 without producing burning or tingling sensations.

1           It is often difficult to predict which compounds will work as permeation  
2 enhancers and which permeation enhancers will work for particular agents.  
3 In systemic drug delivery applications, a compound that enhances the  
4 permeability of one agent or a family of agents may not necessarily enhance  
5 the permeability of another agent or family of agents. Therefore, the  
6 usefulness of a particular compound as a permeation enhancer must be  
7 analyzed carefully.

8           U.S. Patent No. 4,954,487 and European Patent Application 0 043 738  
9 disclose pharmaceutical compositions containing a penetrating vehicle  
10 consisting essentially of a C<sub>1</sub>-C<sub>4</sub> diol compound and a cell envelope  
11 disordering compound. Lauryl acetate is disclosed as a suitable cell envelope  
12 disordering compound.

13           U.S. Patent No. 5,026,556 discloses a composition for the transdermal  
14 delivery of buprenorphine comprising an amount of buprenorphine in a carrier  
15 comprising a polar solvent material selected from the group consisting of  
16 C<sub>3</sub>-C<sub>4</sub> diols, C<sub>3</sub>-C<sub>6</sub> triols, and mixtures thereof; and a polar lipid material  
17 selected from the group consisting of fatty alcohol esters, fatty acid esters,  
18 and mixtures thereof. Lauryl acetate is disclosed as a suitable polar lipid  
19 material.

20           U.S. Patent No. 5,149,538 discloses the transdermal delivery of an  
21 opioid. Preferred permeation enhancers are saturated and unsaturated  
22 fatty alcohols, fatty alcohol esters, or fatty acids having 8-18 carbon atoms.  
23 All of the aforementioned patents are incorporated herein in their entirety  
24 by reference.

25           While it is known in the art to combine permeation enhancers, this  
26 invention utilizes a novel combination of dodecyl acetate (lauryl acetate) and  
27 glycerol monolaurate (GML), and the combined effect is a significant and  
28 surprising improvement over use of GML or lauryl acetate alone.

## DISCLOSURE OF THE INVENTION

It has been found that GML, known to enhance agent permeation in vitro, does not exhibit a good in vitro / in vivo correlation. Results derived from in vivo testing using GML as a permeation enhancer have not been found to be as consistent as the results from in vitro tests. Cosolvents such as lauryl lactate, ethyl lactate, and myristyl lactate all have the potential to effectively enhance agent permeation when combined with GML. However, these combinations of cosolvents and GML perform inconsistently from one lot of formulations to another.

According to this invention, we believe that this inconsistent performance can be attributed to the fact that these cosolvents are not obtainable at a high degree of purity. The lauryl lactate used in the Examples that follow, for example, was obtained as two different mixtures: Ceraphyl 31 or a purer lauryl lactate (both from ISP Van Dyk, Bellevue, NJ). Ceraphyl 31 is a mixture of 50.6% lauryl lactate, 19.1% myristyl lactate, 8.8% lauryl alcohol, 8.3% palmityl lactate, 3.7% stearyl lactate, and 3.5% myristyl alcohol. The purer lauryl lactate is available as a mixture of 82.8% lauryl lactate, 11% lauryl lactyl lactate, and 4% 1-dodecanol.

In addition to the problem of inconsistent performance, the failure to obtain a cosolvent at a high degree of purity also makes it difficult to characterize the system in which the mixture is used. Therefore, cosolvents such as Ceraphyl 31 may not be usable in products subject to regulatory review.

According to this invention, lauryl acetate, a cosolvent obtainable at a high degree of purity, has been found to reduce or eliminate the problems of inconsistency and characterization.

1           Accordingly, the present invention provides a composition of matter  
2   for application to a body surface or membrane to deliver at least one agent,  
3   at a therapeutically effective rate, by permeation through the body surface or  
4   membrane, comprising at least one agent and a permeation-enhancing  
5   amount of lauryl acetate and a monoglyceride or mixture of monoglycerides of  
6   a fatty acid. The invention further provides a method for the transdermal  
7   coadministration of a agent at a therapeutically effective rate together with a  
8   skin permeation-enhancing amount of lauryl acetate and a monoglyceride or  
9   mixture of monoglycerides of a fatty acid. The monoglyceride is preferably  
10  glycerol monolaurate.

11           It is accordingly an aspect of this invention to provide a permeation  
12  enhancer composition for use in transdermal compositions, methods, and  
13  devices which provides for the transdermal coadministration of an agent  
14  at a therapeutically effective rate with improved in vivo efficacy.

15           It is another aspect of this invention to provide a permeation enhancer  
16  composition for use in transdermal compositions, methods, and devices  
17  comprising a monoglyceride and a cosolvent wherein the cosolvent is stable  
18  and obtainable at a high degree of purity, thus resulting in systems which are  
19  more readily characterized.

20           It is yet another aspect of this invention to provide a permeation  
21  enhancer composition for use in transdermal compositions, methods, and  
22  devices which provides consistent results from one lot of formulations to  
23  another.

24           These and other aspects and advantages of this invention will be  
25  readily apparent from the following description with reference to the  
26  accompanying figures.



1                    BRIEF DESCRIPTION OF THE DRAWINGS

2  
3            FIG. 1 is a cross-sectional view of one embodiment of a transdermal  
4 therapeutic agent delivery device which may be used in accordance with the  
5 present invention.

6            FIG. 2 is a cross-sectional view of another embodiment of a  
7 transdermal therapeutic agent delivery device which may be used in  
8 accordance with the present invention.

9            FIG. 3 is a cross-sectional view of yet another embodiment of a  
10 transdermal therapeutic agent delivery device which may be used in  
11 accordance with this invention.

12           FIG. 4 is a cross sectional view of another embodiment of a  
13 transdermal therapeutic agent delivery device which may be used in  
14 accordance with this invention.

15           FIG. 5 is a graph of the flux of alprazolam through human epidermis at  
16 35 °C from systems using various enhancers.

17           FIG. 6 is a graph of the flux of alprazolam through human epidermis at  
18 35 °C from systems using various concentrations of GML with lauryl acetate  
19 or lauryl lactate.

20           FIG. 7 is a graph of the flux of testosterone through human epidermis  
21 at 35 °C from systems using various concentrations of GML with lauryl acetate  
22 or lauryl lactate.

23           FIG. 8 is a graph of the flux of oxybutynin through human epidermis  
24 using various cosolvents for GML.

25           FIG. 9 is a graph of the flux of testosterone through human epidermis  
26 at 35 °C using various formulations of GML with lauryl acetate.

## MODES FOR CARRYING OUT THE INVENTION

According to the invention, GML is combined with lauryl acetate as a cosolvent to provide an improved permeation enhancer mixture. Lauryl acetate, obtainable at 97-99% purity, is effective as a cosolvent for GML and effectively enhances the permeation of various agents through the skin. The combination of lauryl acetate and GML is a potent permeation enhancer mixture which is non-irritating to the skin, provides consistent results, and provides a system which is more readily characterized than other GML/cosolvent mixtures using cosolvents of lower purity.

In addition to its higher degree of purity, lauryl acetate also has greater stability than lauryl lactate and can solubilize a larger amount of GML, thus it may allow for a greater amount of GML to reach the skin. A preferred permeation enhancer composition of this invention comprises lauryl acetate of about 97-99% purity together with GML. It is further preferable that the lauryl acetate of at least 97% purity be used in combination with a monoglyceride containing at least 50% of the principal monoglyceride component and having a monoester content of at least 51%.

It has now been found that a combination of GML and lauryl acetate can be used to effectively enhance the permeability of agents through body surfaces and particularly through the skin. Specifically, it has been found that GML and lauryl acetate enhance the permeability of the skin such that therapeutically effective amounts of an agent can be delivered from reasonably sized devices at therapeutically effective rates.

The system of the invention is preferably a transdermal agent delivery device comprising a matrix adapted to be placed in agent- and permeation enhancer-transmitting relation with the skin or mucosa. The system must be of a size useful for the application of the agent and the enhancer to a human body.

1           The utility of a GML/lauryl acetate dual permeation enhancer has been  
2 demonstrated for a variety of different agents as seen in the Examples that  
3 follow. It is believed that this invention has utility in connection with the  
4 delivery of agents within the broad class normally delivered through body  
5 surfaces and membranes, including skin. In general, this includes therapeutic  
6 agents in all of the major areas, including, but not limited to, ACE inhibitors,  
7 adenohipophyseal hormones, adrenergic neuron blocking agents,  
8 adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical  
9 steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective  
10 alpha-two-adrenergic agonists, analgesics, antipyretics and anti-inflammatory  
11 agents, androgens, local and general anesthetics, antiaddictive agents,  
12 antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic  
13 agents, anticholinesterase agents, anticoagulants, antidiabetic agents,  
14 antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents,  
15 antiepileptic agents, antiestrogens, antifungal agents, antihypertensive  
16 agents, antimicrobial agents, antimigraine agents, antimuscarinic agents,  
17 antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet  
18 agents, antiprogestins, antithyroid agents, antitussives, antiviral agents,  
19 atypical antidepressants, azaspirodecanediones, barbituates,  
20 benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-  
21 adrenergic antagonists, selective beta-one-adrenergic antagonists, selective  
22 beta-two-adrenergic agonists, bile salts, agents affecting volume and  
23 composition of body fluids, butyrophenones, agents affecting calcification,  
24 calcium channel blockers, cardiovascular drugs, catecholamines and  
25 sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators,  
26 dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids,  
27 estrogens, ganglionic blocking agents, ganglionic stimulating agents,  
28 hydantoins, agents for control of gastric acidity and treatment of peptic  
29 ulcers, hematopoietic agents, histamines, histamine antagonists,

1 5-hydroxytryptamine antagonists, drugs for the treatment of  
2 hyperlipoproteinemia, hypnotics and sedatives, immunosuppressive agents,  
3 laxatives, methylxanthines, monoamine oxidase inhibitors, neuromuscular  
4 blocking agents, organic nitrates, opioid analgesics and antagonists,  
5 pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for  
6 the treatment of psychiatric disorders, retinoids, sodium channel blockers,  
7 agents for spasticity and acute muscle spasms, succinimides, thioxanthines,  
8 thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of  
9 tubular transport of organic compounds, drugs affecting uterine motility,  
10 vasodilators, vitamins and the like.

11 Representative agents include, by way of example and not for  
12 purposes of limitation, bepridil, diltiazem, felodipine, isradipine, nicardipine,  
13 nifedipine, nimodipine, nitredipine, verapamil, dobutamine, isoproterenol,  
14 carterolol, labetalol, levobunolol, nadolol, penbutolol, pindolol, propranolol,  
15 sotalol, timolol, acebutolol, atenolol, betaxolol, esmolol, metoprolol, albuterol,  
16 bitolterol, isoetharine, metaproterenol, pirbuterol, ritodrine, terbutaline,  
17 alclometasone, aldosterone, amcinonide, beclomethasone dipropionate,  
18 betamethasone, clobetasol, clocortolone, cortisol, cortisone, corticosterone,  
19 desonide, desoximetasone, 11-desoxycorticosterone, 11-desoxycortisol,  
20 dexamethasone, diflorasone, fludrocortisone, flunisolide, fluocinolone,  
21 fluocinonide, fluorometholone, flurandrenolide, halcinonide, hydrocortisone,  
22 medrysone, 6 $\alpha$ -methylprednisolone, mometasone, paramethasone,  
23 prednisolone, prednisone, tetrahydrocortisol, triamcinolone, benoxinate,  
24 benzocaine, bupivacaine, chloroprocaine, cocaine, dibucaine, dyclonine,  
25 etidocaine, lidocaine, mepivacaine, pramoxine, prilocaine, procaine,  
26 proparacaine, tetracaine, alfentanil, chloroform, clonidine, cyclopropane,  
27 desflurane, diethyl ether, droperidol, enflurane, etomidate, fentanyl,  
28 halothane, isoflurane, ketamine hydrochloride, meperidine, methohexital,  
29 methoxyflurane, morphine, propofol, sevoflurane, sufentanil, thiamylal,

1 thiopental, acetaminophen, allopurinol, apazone, aspirin, auranofin,  
2 aurothioglucose, colchicine, diclofenac, diflunisal, etodolac, fenoprofen,  
3 flurbiprofen, gold sodium thiomalate, ibuprofen, indomethacin, ketoprofen,  
4 meclofenamate, mefenamic acid, meselamine, methyl salicylate,  
5 nabumetone, naproxen, oxyphenbutazone, phenacetin, phenylbutazone,  
6 piroxicam, salicylamide, salicylate, salicylic acid, salsalate, sulfasalazine,  
7 sulindac, tolmetin, acetophenazine, chlorpromazine, fluphenazine,  
8 mesoridazine, perphenazine, thioridazine, trifluorperazine, triflupromazine,  
9 disopyramide, encainide, flecainide, indecainide, mexiletine, moricizine,  
10 phenytoin, procainamide, propafenone, quinidine, tocainide, cisapride,  
11 domperidone, dronabinol, haloperidol, metoclopramide, nabilone,  
12 prochlorperazine, promethazine, thiethylperazine, trimethobenzamide,  
13 buprenorphine, butorphanol, codeine, dezocine, diphenoxylate, drocode,  
14 hydrocodone, hydromorphone, levallorphan, levorphanol, loperamide,  
15 meptazinol, methadone, nalbuphine, nalmeferene, nalorphine, naloxone,  
16 naltrexone, oxybutynin, oxycodone, oxymorphone, pentazocine,  
17 propoxyphene, isosorbide dinitrate, nitroglycerin, theophylline, phenylephrine,  
18 ephedrine, pilocarpine, furosemide, tetracycline, chlorpheniramine, ketorolac,  
19 bromocriptine, guanabenz, prazosin, doxazosin, and flufenamic acid.

20 Other representative agents include benzodiazepines, such as  
21 alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam,  
22 clorazepate, demoxepam, diazepam, flumazenil, flurazepam, halazepam,  
23 lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam,  
24 quazepam, temazepam, triazolam, and the like; an antimuscarinic agent such  
25 as anisotropine, atropine, clidinium, cyclopentolate, dicyclomine, flavoxate,  
26 glycopyrrolate, hexocyclium, homatropine, ipratropium, isopropamide,  
27 mepenzolate, methantheline, oxyphencyclimine, pirenzepine, propantheline,  
28 scopolamine, telenzepine, tridihexethyl, tropicamide, and the like; an estrogen  
29 such as chlorotrianisene, siethylstilbestrol, methyl estradiol, estrone, estrone

1 sodium sulfate, estropipate, mestranol, quínestrol, sodium equilin sulfate,  
2 17 $\beta$ -estradiol (or estradiol), semi-synthetic estrogen derivatives such as the  
3 esters of natural estrogen, such as estradiol-17 $\beta$ -enanthate, estradiol-17 $\beta$ -  
4 valerate, estradiol-3-benzoate, estradiol-17 $\beta$ -undecenoate, estradiol 16,  
5 17-hemisuccinate or estradiol-17 $\beta$ -cypionate, and the 17-alkylated estrogens,  
6 such as ethinyl estradiol, ethinyl estradiol-3- isopropylsulphonate, and the  
7 like; an androgen such as danazol, fluoxymesterone, methandrostenolone,  
8 methyltestosterone, nandrolone, nandrolone decanoate, nandrolone  
9 phenpropionate, oxandrolone, oxymetholone, stanozolol, testolactone,  
10 testosterone, testosterone cypionate, testosterone enanthate, testosterone  
11 propionate, and the like; or a progestin such as ethynodiol diacetate,  
12 gestodene, hydroxyprogesterone caproate, levonorgestrel,  
13 medroxyprogesterone acetate, megestrol acetate, norethindrone,  
14 norethindrone acetate, norethynodrel, norgestrel, progesterone, and the like.

15 Lauryl acetate has been demonstrated herein as a suitable cosolvent  
16 for GML. Lauryl acetate may also be used as a cosolvent together with  
17 other monoglycerides. Typically, monoglycerides have been available as a  
18 mixture of monoglycerides of fatty acids with one monoglyceride being the  
19 principal component, from which component the mixture derives its name.  
20 For example, one commercial monoglyceride is Emerest 2421 glycerol  
21 monooleate (Emery Division, Quantum Chemical Corp.), which is a mixture  
22 of glycerol oleates with a glycerol monooleate content of 58% by weight and  
23 a total monoesters content of 58% by weight.

24 Other examples of commercial monoglycerides are Myverol 1899K  
25 glycerol monooleate (Eastman Chemical Products) which has a glycerol  
26 monooleate content of 61% and a total monoesters content of 93%,  
27 and Myverol 1892K glycerol monolinoleate which has a glycerol  
28 monolinoleate content of 68% and a minimum total monoesters content

1 of 90%. The monoesters are chosen from those with from 10 to 20 carbon  
2 atoms. The fatty acids may be saturated or unsaturated and include,  
3 for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid and  
4 palmitic acid. Monoglyceride permeation enhancers include glycerol  
5 monooleate, glycerol monolaurate and glycerol monolinoleate, for example.

6 Transdermal agent delivery systems are typically maintained in  
7 contact with the skin using an "in-line" contact adhesive, ie, a layer of  
8 adhesive positioned between the agent reservoir of the delivery system and  
9 the skin. Glycerol monooleate having a total monoesters content of less than  
10 about 65% interacts adversely with known adhesive materials to such an  
11 extent that the adhesive cannot function to maintain a delivery device on the  
12 skin. Therefore, when an in-line adhesive is present as a part of the device  
13 of the invention so that a permeation enhancer must pass through the  
14 adhesive, and when glycerol monooleate is utilized as the second permeation  
15 enhancer, the glycerol monooleate must have a total monoesters content of  
16 at least 65%.

17 Administration of the agent according to the invention comprises  
18 administering the agent at a therapeutically effective rate to an area of a body  
19 surface (eg, skin) or membrane and simultaneously administering GML and  
20 lauryl acetate to the area of the body surface or membrane at rates which are  
21 sufficient to substantially increase the permeability of the area to the agent  
22 formulation.

23 According to the invention, the GML and lauryl acetate mixture and the  
24 agent to be delivered are placed in agent- and permeation enhancer-  
25 transmitting relationship to the appropriate body surface, preferably in a  
26 carrier therefor, and maintained in place for the desired period of time.  
27 The agent and permeation enhancer mixture are typically dispersed within a  
28 physiologically compatible matrix or carrier which may be applied directly to

1 the body surface or skin as an ointment, gel, cream, suppository or sublingual  
2 or buccal tablet, for example, but are more preferably administered from  
3 a transdermal therapeutic delivery device as more fully described below.  
4 When used in the form of a liquid, ointment, cream, or gel applied directly  
5 to the skin, it is preferable, although not required, to occlude the site of  
6 administration. Such compositions can also contain other permeation  
7 enhancers, stabilizers, dyes, diluents, pigments, vehicles, inert fillers,  
8 excipients, gelling agents, vasoconstrictors, and other components of typical  
9 compositions as are known to the art.

10 The GML/lauryl acetate dual permeation enhancer of this invention has  
11 a permeation-enhancing effect on the transport of agents through body  
12 surface tissues generally, in addition to the skin. However, because skin is  
13 one of the most effective barriers to the permeation of agents into the body,  
14 the effect of GML and lauryl acetate on skin permeation makes it extremely  
15 useful in transdermal delivery. The following description of embodiments of  
16 the invention is therefore directed primarily to improving systemic delivery of  
17 these agents by permeation through the skin.

18 One embodiment of a transdermal delivery device of the present  
19 invention is illustrated in FIG. 1. In FIG. 1, device 1 is comprised of a agent-  
20 and permeation enhancer-containing reservoir ("agent reservoir") 2 which is  
21 preferably in the form of a matrix containing the agent and the enhancer  
22 dispersed therein. An impermeable backing layer 3 is provided adjacent one  
23 surface of agent reservoir 2. Adhesive overlay 4 maintains the device 1 on  
24 the skin and may be fabricated together with, or provided separately from,  
25 the remaining elements of the device. With certain formulations, the adhesive  
26 overlay 4 may be preferable to an in-line contact adhesive, such as adhesive  
27 layer 28 as shown in FIG. 3. Impermeable backing layer 3 is preferably  
28 slightly larger than agent reservoir 2, and in this manner prevents the



1 materials in agent reservoir 2 from adversely interacting with the adhesive in  
2 overlay 4. A strippable or removable liner 5 is also provided with device 1  
3 and is removed just prior to application of device 1 to the skin.

4 Figure 2 illustrates another embodiment of the invention, device 10,  
5 shown in placement on the skin 17. In this embodiment, the transdermal  
6 agent delivery device 10 comprises multi-laminate agent  
7 formulation/enhancer reservoir 11 having at least two zones 12 and 14.  
8 Zone 12 consists of an agent reservoir substantially as described with respect  
9 to FIG. 1. Zone 14 comprises a permeation enhancer reservoir which is  
10 preferably made from substantially the same matrix as is used in zone 12.  
11 Zone 14 comprises GML and lauryl acetate dispersed throughout and is  
12 substantially free of any undissolved agent. A rate-controlling membrane 13  
13 for controlling the release rate of the GML/lauryl acetate mixture from zone 14  
14 to zone 12 is placed between the two zones. A rate-controlling membrane  
15 (not shown) for controlling the release rate of the enhancer from zone 12 to  
16 the skin may also optionally be utilized and would be present between the  
17 skin 17 and zone 12.

18 The rate-controlling membrane 13 may be fabricated from permeable,  
19 semipermeable or microporous materials which are known in the art to control  
20 the rate of agents into and out of delivery devices and having a permeability  
21 to the permeation enhancer lower than the matrix material of zone 12.  
22 Suitable materials include, but are not limited to, polyethylene, polyvinyl  
23 acetate and ethylene vinyl acetate copolymers.

24 An advantage of the device described in FIG. 2 is that the agent-  
25 loaded zone 12 is concentrated at the skin surface rather than throughout the  
26 entire mass of a combined agent and enhancer reservoir such as reservoir 2  
27 in FIG. 1. This reduces the amount of agent in the device while maintaining  
28 an adequate supply of permeation enhancer.

1 Superimposed over the agent formulation/enhancer reservoir 11/12  
2 of device 10 is an impermeable backing 15 and an adhesive overlay 16  
3 as described above with respect to FIG. 1. In addition, a strippable liner  
4 (not shown) would preferably be provided on the device prior to use as  
5 described with respect to FIG. 1 and removed prior to application of the  
6 device 10 to the skin 17.

7 In the embodiments of FIGS. 1 and 2, the carrier or matrix material  
8 has sufficient viscosity to maintain its shape without oozing or flowing.  
9 If, however, the matrix or carrier is a low viscosity flowable material,  
10 the composition can be fully enclosed in a permeable or microporous  
11 skin-contacting membrane, as known to the art from U.S. Patent  
12 No. 4,379,454 (noted above), for example.

13 Another embodiment is illustrated in FIG. 3. Device 20 comprises an  
14 agent reservoir 22 containing both the agent and the GML/lauryl acetate  
15 permeation enhancer. Reservoir 22 is preferably in the form of a matrix  
16 containing the agent and the enhancer dispersed therein. Reservoir 22 is  
17 sandwiched between a backing layer 24, which is preferably impermeable to  
18 both the agent and the permeation enhancer mixture, and an in-line contact  
19 adhesive layer 28. In FIG. 3, the agent reservoir 22 is formed of a material,  
20 such as a rubbery polymer, that is sufficiently viscous to maintain its shape.  
21 The device 20 adheres to the surface of the skin 17 by means of the contact  
22 adhesive layer 28. The adhesive for layer 28 should be chosen so that it is  
23 compatible and does not interact with any of the agent or, in particular,  
24 the GML/lauryl acetate permeation enhancer. The adhesive layer 28 may  
25 optionally contain enhancer and/or agent. A strippable liner (not shown)  
26 is normally provided along the exposed surface of adhesive layer 28 and is  
27 removed prior to application of device 20 to the skin 17. In an alternative  
28 embodiment, a rate-controlling membrane (not shown) is present and

1 the agent reservoir 22 is sandwiched between backing layer 24 and the  
2 rate-controlling membrane, with adhesive layer 28 present on the skin-side of  
3 the rate-controlling membrane.

4 Various materials suited for the fabrication of the various layers of the  
5 transdermal devices of FIGS. 1-3 are known in the art or are disclosed in the  
6 aforementioned transdermal device patents previously incorporated herein by  
7 reference.

8 The matrix making up the agent / permeation enhancer reservoir of  
9 Figures 1-3 can be a gel or a polymer. Suitable materials are compatible  
10 with the agent, GML or other monoglyceride, lauryl acetate, and any other  
11 components in the system. Suitable matrix materials include, without  
12 limitation, natural and synthetic rubbers or other polymeric material, thickened  
13 mineral oil, or petroleum jelly, for example. The matrix is preferably polymeric  
14 and is more preferably an anhydrous polymer. A preferred embodiment  
15 according to this invention is fabricated from an ethylene vinyl acetate (EVA)  
16 copolymer, of the type described in U.S. Patent No. 4,144,317, and is  
17 preferably selected from those EVAs having a vinyl acetate (VA) content in  
18 the range of about 9 to 60%, preferably about 28 to 60% VA. Particularly  
19 good results may be obtained using EVA of 40% vinyl acetate content.

20 In addition to an agent and GML/lauryl acetate, which are essential to  
21 the invention, the matrix, if needed, may also contain stabilizers, dyes,  
22 pigments, inert fillers, tackifiers, excipients and other conventional  
23 components of transdermal delivery devices as are known in the art.

24 Figure 4 depicts another preferred embodiment of the present  
25 invention. Device 30 includes a matrix 31 having agent and the GML / lauryl  
26 acetate permeation enhancer mixture dispersed therein and can additionally  
27 include a backing layer 32 to contain the agent and prevent its loss. Matrix 31  
28 also preferably, but not necessarily, contains a water absorbing polymer to

1 improve the long term wearability of the matrix system. A release liner  
2 (not shown in Figure 4) may also be included and is removed prior to placing  
3 the device onto the skin 17.

4 The matrix material 31 comprises a hydrophobic pressure sensitive  
5 adhesive and preferably comprises a polysiloxane adhesive. The water  
6 absorbing polymers useful with the present invention are known in the art and  
7 include, for example, polyvinyl pyrrolidone, cross-linked polyvinyl pyrrolidone,  
8 polyaminoacrylates, and polyvinyl alcohol. Polyvinyl pyrrolidone is preferred.

9 The backing layer 32 is an elastomeric sheet or film that is substantially  
10 impermeable to the selected agent and permeation enhancers and has a  
11 thickness of about 1 micrometer to 100 micrometers. Suitable backing  
12 materials are known in the art and include, for example, low or medium  
13 density polyethylene, polypropylene, polyesters, and silicone elastomers.

14 According to a preferred embodiment of the matrix system depicted  
15 in Figure 4, device 30 is prepared by extruding and calendering the adhesive  
16 composition between two differential release substrates. One of these  
17 release substrates is subsequently removed and the system is laminated to a  
18 backing layer.

19 Hot melt processing of the adhesive composition is accomplished by  
20 adding to the polysiloxane adhesive, which is dissolved in a carrier solvent,  
21 excipients which can plasticize the polysiloxane adhesive. This enables the  
22 excipients to be finely mixed into the solution. The carrier solvent is  
23 subsequently evaporated off, resulting in a pressure sensitive adhesive that  
24 is already plasticized by the excipients. The adhesive can then be mixed  
25 with additional excipients, such as active agents and water absorbing  
26 polymers, using blending equipment known in the art and subsequently  
27 hot melt processed in manufacturing.

1           According to this preferred embodiment, the plasticizing excipients are  
2 permeation enhancers which are capable of plasticizing the polysiloxane  
3 adhesive to a much lower complex viscosity and significantly lower the  
4 viscosity at time scales corresponding to process shear rates, typically of  
5 about 100 rad/sec. Suitable complex dynamic viscosities for the extrudable  
6 adhesive composition range from  $10^3$  -  $10^7$  Poise, depending upon the  
7 processing temperature and shear rate. Glycerol monolaurate and lauryl  
8 acetate are the preferred plasticizing excipients.

9           The amounts of the agent that are present in the therapeutic devices  
10 depicted in Figures 1-4 required to achieve a therapeutic effect depend on  
11 many factors, such as the minimum necessary dosage of the particular agent;  
12 the permeability of the matrix, of the adhesive layer and of the rate-controlling  
13 membrane, if present; and the period of time for which the device will be fixed  
14 to the skin. There is, in fact, no upper limit to the maximum amounts of agent  
15 present in the device. The minimum amount of each agent is determined by  
16 the requirement that sufficient quantities of agent must be present in the  
17 device to maintain the desired rate of release over the given period of  
18 application.

19           The agent is generally dispersed through the matrix at a concentration  
20 in excess of saturation, i.e. at unit activity. The amount of excess is  
21 determined by the intended useful life of the system. However, the agent  
22 may be present at initial levels below saturation without departing from this  
23 invention. Generally, the agent may be present at initially subsaturated levels  
24 when: 1) the skin flux of the agent is sufficiently low such that the reservoir  
25 agent depletion is slow and small; 2) non-constant delivery of the agent is  
26 desired or acceptable; and/or 3) saturation of the reservoir is achieved in use  
27 due to migration of water into the reservoir from the skin, where water is  
28 abundantly available.

1           The GML and lauryl acetate mixture is dispersed throughout the  
2 matrix, preferably at a concentration sufficient to provide permeation--  
3 enhancing concentrations of enhancer in the reservoir throughout the  
4 anticipated administration period.

5           In the present invention, the agent is delivered through the skin  
6 or other body surface at a therapeutically effective rate (that is, a rate  
7 that provides an effective therapeutic result) and the GML/lauryl acetate  
8 dual permeation enhancer is delivered at a permeation-enhancing rate  
9 (that is, a rate that provides increased permeability of the application site  
10 to the agent) for a predetermined time period.

11           A preferred embodiment of the present invention is a device such as  
12 that illustrated in FIG. 3 (either with or without a rate-controlling membrane)  
13 wherein reservoir 22 comprises, by weight, 30- 80% polymer (preferably  
14 EVA having a vinyl acetate content of 40%), 0.1-30% agent, 1-40% GML,  
15 and 1-40% lauryl acetate. The in-line adhesive layer 28 comprises an  
16 adhesive which is compatible with the permeation enhancer. A particularly  
17 preferred embodiment is a device as described above wherein the  
18 permeation enhancer mixture of glycerol monolaurate and lauryl acetate  
19 comprises 20% GML and 12% lauryl acetate.

20           Another preferred embodiment of the present invention is a matrix  
21 system such as that illustrated in Fig. 4 wherein the matrix comprises,  
22 by weight, 40-90% polymer (preferably a polysiloxane adhesive), 0.1-25%  
23 polyvinyl pyrrolidone, 0.1-30% agent, 1-30% GML, and 1-30% lauryl acetate.

24           The devices of this invention can be designed to effectively deliver a  
25 agent for an extended time period of up to 7 days or longer. Seven days  
26 is generally the maximum time limit for application of a single device  
27 because the skin site is adversely affected by a period of occlusion greater  
28 than 7 days. Where it is desired to have agent delivery for greater than

1 7 days (such as, for example, when a hormone is being applied for a  
2 contraceptive effect), when one device has been in place on the skin for its  
3 effective time period, it is replaced with a fresh device, preferably on a  
4 different skin site.

5 The transdermal therapeutic devices of the present invention are  
6 prepared in a manner known in the art, such as by those procedures,  
7 for example, described in the transdermal device patents listed previously  
8 herein. The following examples are offered to illustrate the practice of the  
9 present invention and are not intended to limit the invention in any manner.

10

11 EXAMPLE 1

12

13 The effect of various permeation enhancer mixtures on the transdermal  
14 flux of alprazolam was studied. The agent/permeation enhancer reservoirs  
15 were prepared by mixing ethylene vinyl acetate having a vinyl acetate content  
16 of 40 percent ("EVA 40", USI Chemicals, Illinois) in an internal mixer  
17 (Brabender type) until the EVA 40 pellets fused. Alprazolam, GML, glycerol  
18 monooleate (GMO), lauryl acetate (Penta International Corp., Livingston, NJ),  
19 lauryl lactate, and myristyl lactate were then added as shown in Table 1.  
20 The mixture was blended, cooled, and calendered to a 5 mil thick film.

21 The film was then laminated to a Medpar® (3M, St. Paul, Mn) backing  
22 on one side and an acrylate contact adhesive (3M Acrylic MSP 041991P)  
23 on the opposite side. The laminate was then cut into 2.54 cm<sup>2</sup> circles using a  
24 steel punch.

TABLE 1

Agent/Permeation Enhancer Reservoir Composition (weight percent)

FORMULATION	WEIGHT PERCENT
Alprazolam/GML/lauryl acetate/EVA 40	15/20/12/53
Alprazolam/GML/lauryl lactate/EVA 40	15/20/12/53
Alprazolam/GML/lauryl lactate/EVA 40	15/13/27/45
Alprazolam/GMO/EVA 40	15/30/55
Alprazolam/GMO/lauryl lactate/EVA 40	15/20/12/53
Alprazolam/GMO/myristyl lactate/EVA 40	15/20/12/53

Circular pieces of human epidermis were mounted on the receptor compartment of horizontal permeation cells with the stratum corneum facing the donor compartment of the cell. The release liner of the laminate was removed and the systems were centered over the stratum corneum side of the epidermis. The donor compartment was then clamped with the receptor compartment. A known volume of receptor solution (20 ml, 0.01M potassium phosphate pH 6 + 2% isopropyl alcohol) was equilibrated at 35 °C and placed in the receptor compartment. Air bubbles were removed from the receptor compartment, the cell was capped and placed in a water bath shaker at 35 °C.

At given time intervals, the entire receptor solution was removed from the cells and replaced with an equal volume of fresh receptor solutions previously equilibrated at 35 °C. The receptor solutions are stored in capped vials at 4 °C until assayed for alprazolam content by high performance liquid chromatography (HPLC). From the agent concentration and the volume of the receptor solutions, the area of permeation and the time interval, the flux of the agent through the epidermis was calculated as follows: (agent concentration x volume of receptor)/(area x time) = flux ( $\mu\text{g}/\text{cm}^2 \cdot \text{hr}$ ).



1 The transdermal fluxes of the various systems is shown in Figure 5.  
2 As demonstrated in Figure 5, the system comprising the GML/lauryl acetate  
3 permeation enhancer mixture achieved the greatest flux of alprazolam  
4 through skin.

## 6 EXAMPLE 2

8 The effect of GML and various cosolvents on the transdermal flux of  
9 oxybutynin was determined. The agent/permeation enhancer reservoirs,  
10 having the compositions shown in Table 2, were prepared by the procedure  
11 described in Example 1.

12 TABLE 2

14 Agent/Permeation Enhancer Reservoir Composition (weight percent)

AGENT RESERVOIR	WEIGHT PERCENT
oxybutynin base/GML/EVA	25/20/55
oxybutynin base/GML/ceraphyl 31/EVA	25/20/12/43
oxybutynin base/GML/lauryl lactate/EVA	25/20/12/43
oxybutynin base/GML/methyl laurate/EVA	25/20/12/43
oxybutynin base/GML/lauryl acetate/EVA	25/20/12/43

15  
16 The agent reservoirs were then laminated to a water vapor permeable  
17 Sontara® spun laced polyester backing (code 80632B, DuPont, Wilmington  
18 DE) on one side and a 1 mil thick Celgard® (Hoechst Celanese, Charlotte,  
19 NC) film tie layer (microporous polypropylene) on the other. The laminate  
20 was then cut into 1.98 cm<sup>2</sup> circles using a steel punch. The punched systems  
21 were then weighed and placed in a 35 °C oven to equilibrate.

1       The in vitro transdermal oxybutynin permeation rates through human  
2 epidermis from the systems described above were determined. The systems  
3 tested were masked so that none of the device, except for the skin contacting  
4 surface, would be exposed to the receptor solution. For each system tested,  
5 the release liner was removed and the oxybutynin-releasing surface was  
6 centered and placed against the stratum corneum side of a disc of human  
7 epidermis which had been blotted dry just prior to use. The excess epidermis  
8 was wrapped around the device.

9       The assembly was then attached to the flat side of a Teflon® holder of  
10 a release rate rod using wire and nylon mesh. The rod with the system  
11 attached was placed into a 50 cc test tube filled with a known volume of  
12 receptor solution (0.05M phosphate solution, pH 6.0). Constant vertical  
13 stirring was accomplished by attaching the rod to a crossrod connected to an  
14 agitator that reciprocates the rod and system vertically in the test tube.  
15 The receptor solution was maintained at 35 °C.

16       At given time intervals, the entire receptor solution was removed from  
17 the test tube and replaced with an equal volume of fresh receptor solution  
18 previously equilibrated at 35 °C. The receptor solutions were stored in  
19 capped vials and refrigerated until assayed for oxybutynin content by HPLC.

20       The transdermal flux of oxybutynin through human epidermis from  
21 these systems is shown in Figure 6. As demonstrated in Figure 6, the  
22 resultant skin flux of the GML/lauryl acetate formulation was greater than  
23 that of GML alone.

EXAMPLE 3

Systems comprising permeation enhancer mixtures of GML/lauryl acetate were compared to systems comprising mixtures of GML/lauryl lactate to observe the effect on the transdermal flux of alprazolam. Agent/permeation enhancer reservoirs, having the compositions shown in Table 3, were prepared by the procedures described in Example 1.

These reservoir formulations were then used in transdermal flux studies using the same apparatus and procedures described in Example 1. The effect of the concentration of GML, lauryl acetate, and lauryl lactate on the flux of alprazolam through human epidermis from EVA 40 monoliths at 35 °C is shown in Figure 7. As demonstrated in Figure 7, the GML/lauryl acetate mixture provided a superior flux of alprazolam through skin of up to three times that of a GML/lauryl lactate mixture. The 15/25 mixture of GML/lauryl acetate reached steady state flux the quickest.

TABLE 3

Agent/Permeation Enhancer Reservoir Composition (weight percent)

FORMULATION	WEIGHT PERCENT
Alprazolam/GML/lauryl acetate/EVA 40	15/20/12/53
Alprazolam/GML/lauryl acetate/EVA 40	15/13/27/45
Alprazolam/GML/lauryl acetate/EVA 40	15/15/25/45
Alprazolam/GML/lauryl lactate/EVA 40	15/20/12/53
Alprazolam/GML/lauryl lactate/EVA 40	15/13/27/45
Alprazolam/GML/lauryl lactate/EVA 40	15/15/25/45
Alprazolam/EVA 40	15/85

**EXAMPLE 4**

Agent/permeation enhancer reservoirs were prepared using the procedure of Example 3, substituting testosterone for alprazolam. The composition of the agent reservoirs is shown in Table 4.

**TABLE 4**

Agent/Permeation Enhancer Reservoir Composition (weight percent)

FORMULATION	WEIGHT PERCENT
Testosterone/GML/lauryl acetate/EVA 40	15/20/12/53
Testosterone /GML/lauryl acetate/EVA 40	15/13/27/45
Testosterone /GML/lauryl acetate/EVA 40	15/15/25/45
Testosterone /GML/lauryl lactate/EVA 40	15/20/12/53
Testosterone /GML/lauryl lactate/EVA 40	15/13/27/45
Testosterone /GML/lauryl lactate/EVA 40	15/15/25/45
Testosterone /EVA 40	15/85

The skin flux experiment described in Example 1 was repeated for these systems, substituting 0.1% phenol as the receptor solution. The effect of the concentration of GML, lauryl acetate, and lauryl lactate on the flux of testosterone through human epidermis from EVA 40 monoliths at 35 °C is shown in Figure 8.

EXAMPLE 5

A matrix type system according to Figure 4 was prepared according to the following procedure. GML and lauryl acetate were mixed in a polysiloxane adhesive solution (XT-4502, Dow Corning). In a separate step, polyvinyl pyrrolidone (PVP) (Povidone, ISP Van Dyk, Bellevue, NJ) was dissolved in ethanol. Testosterone was then added to the ethanol/PVP solution and the resultant solution was mixed for approximately one hour. This solution was then added to the GML / lauryl acetate / polysiloxane solution. The resulting solution was heated to approximately 50° C and mixed for a few hours until a fine white dispersion was obtained. The dispersion was then cast onto a backing (CoTrans 9720, 3M) to a wet thickness of about 10-17 mils. The solution was then heated in a drying oven at 70° C for approximately one hour. The resulting cast was 3-5 mils thick and was laminated to a release liner (FDC/PET, 3M - 1022) 2.5 cm<sup>2</sup> circular pieces were then die cut and used in the *in vitro* skin flux experiments according to Example 1. The compositions of the formulations made according to this procedure are shown in Table 5. Each of the formulations contained testosterone at a concentration in the matrix in excess of saturation.

TABLE 5

Matrix Composition (weight percent)

FORMULATION	WEIGHT PERCENT
GML/lauryl acetate/testosterone/polysiloxane	10/10/2/78
GML/ lauryl acetate/PVP/testosterone/polysiloxane	10/10/10/2/68
GML/lauryl acetate/PVP/testosterone/polysiloxane	2/10/10/2/76
testosterone/EVA 40	2/98

1           The skin flux experiment described in Example 1 was repeated for  
2 these systems, substituting 0.1% phenol as the receptor solution. The effect  
3 of the concentration of GML and lauryl acetate on the flux of testosterone  
4 through human epidermis from matrix systems at 35 °C is shown in Figure 9.  
5 As seen in Figure 9, formulations including GML and lauryl acetate resulted in  
6 a 4-10 fold increase in flux over the EVA 40 control without enhancers.

7           The invention has been described in detail with particular reference to  
8 certain preferred embodiments thereof, but it will be understood that  
9 variations and modifications can be affected within the scope and spirit of the  
10 invention.

1   What is claimed is:

2           1.    A composition of matter for transdermally delivering a  
3   biologically active agent at a therapeutically effective rate by permeation  
4   through a body surface or membrane comprising, in combination:

5           (a) a biologically active agent; and

6           (b) a permeation-enhancing amount of a dual permeation enhancer  
7   comprising lauryl acetate and a monoglyceride, wherein the agent and  
8   permeation enhancer are dispersed within a carrier.

9           2.    A composition according to claim 1 wherein the monoglyceride  
10   is glycerol monolaurate.

11          3.    A composition according to claim 1 wherein the agent is present  
12   in an amount in excess of its saturation in the carrier.

13          4.    A composition according to claim 1 wherein the lauryl acetate is  
14   at least 97% pure.

15          5.    A pressure sensitive adhesive composition for the transdermal  
16   administration of a biologically active agent comprising, by weight:

17           (a) 0.1-30% of a biologically active agent,

18           (b) 30-90% of a polysiloxane adhesive,

19           (c) 1-40% of a permeation enhancer capable of plasticizing the  
20   polysiloxane adhesive.

21          6.    A composition according to claim 5 wherein the composition is a  
22   hot melt pressure sensitive adhesive.

23          7.    A composition according to claim 6 comprising a viscosity within  
24   the range of  $10^3$  -  $10^7$  Poise.

25          8.    A composition according to claim 7 comprising a viscosity within  
26   the range of  $2 \times 10^5$  -  $10^6$  of the Poise.

27          9.    A composition according to claim 5 wherein the permeation  
28   enhancer comprises glycerol monolaurate, lauryl acetate, or a mixture  
29   thereof.

1           10.    A composition according to claim 9 wherein the composition  
2    comprises 1-30% glycerol monolaurate and 1-30% by weight lauryl acetate.

3           11.    A composition according to claim 9 further comprising 1-30% by  
4    weight of a water absorbing polymer.

5           12.    A composition according to claim 11 wherein the water  
6    absorbing polymer is polyvinyl pyrrolidone.

7           13.    A device for the transdermal administration of an agent at a  
8    therapeutically effective rate by permeation through a body surface or  
9    membrane, comprising:

10          a) an agent reservoir comprising an agent and a permeation-  
11    enhancing amount of a permeation enhancer mixture comprising lauryl  
12    acetate and a monoglyceride;

13          b) a backing behind the skin distal surface of the agent reservoir;

14          c) means for maintaining the reservoir in agent- and permeation  
15    enhancer -transmitting relation with the body surface or membrane.

16          14.    A device according to claim 13 wherein the monoglyceride is  
17    glycerol monolaurate.

18          15.    A device according to claim 13 wherein the agent is oxybutynin.

19          16.    A device according to claim 13 wherein the agent is  
20    testosterone.

21          17.    A device according to claim 13 wherein the agent is nandrolone.

22          18.    A device according to claim 13 wherein the means for  
23    maintaining the reservoir in agent- and permeation enhancer -transmitting  
24    relation with the body surface or membrane is a contact adhesive.



1           19.    A device according to claim 13 wherein the agent reservoir  
2 comprises:

- 3                   i) .1-30% by weight of an agent,  
4                   ii) 5-40% by weight lauryl acetate,  
5                   iii) 5-40% by weight glycerol monolaurate, and  
6                   iv) 30-60% by weight ethylene vinyl acetate copolymer.

7           20.    A device according to claim 19 wherein the agent reservoir  
8 comprises 20% GML and 12% lauryl acetate.

9           21.    A device according to claim 13 wherein the lauryl acetate is at  
10 least 97% pure.

11          22.    A device for the transdermal administration of an agent at a  
12 therapeutically effective rate by permeation through a body surface or  
13 membrane, comprising:

14               a) a first reservoir comprising an agent and a permeation-enhancing  
15 amount of a permeation enhancer mixture comprising lauryl acetate and a  
16 monoglyceride;

17               b) a second reservoir comprising an additional amount of the  
18 permeation enhancer mixture;

19               c) a rate controlling membrane between the first and second  
20 reservoirs;

21               d) a backing behind the skin distal surface of the first reservoir; and

22               e) means for maintaining the reservoir in agent- and permeation  
23 enhancer -transmitting relation with the body surface or membrane.

24          23.    A device according to claim 22 wherein the monoglyceride is  
25 glycerol monolaurate.

26          24.    A device according to claim 22 wherein the agent is oxybutynin.

27          25.    A device according to claim 22 wherein the agent is  
28 testosterone.

1           26.    A device according to claim 22 wherein the agent is nandrolone.

2           27.    A device according to claim 22 wherein the lauryl acetate is at  
3    least 97% pure.

4           28.    A device for the transdermal administration of a biologically  
5    active agent at a therapeutically effective rate comprising:

6                   (a) a backing layer, and

7                   (b) an agent reservoir matrix comprising a polymeric blend  
8    comprising, by weight:

9                           (i) 40-90% of a silicone adhesive,

10                          (ii) 1-30% of a water absorbing polymer,

11                          (iii) 0.1-30% agent,

12                          (iv) a permeation enhancer comprising 1-30% of a  
13    monoglyceride and 1-30% lauryl acetate.

14           29.    A device according to claim 28 wherein the monoglyceride is  
15    glycerol monolaurate.

16           30.    A device according to claim 29 wherein the water absorbing  
17    polymer is selected from the group consisting of polyvinyl pyrrolidone,  
18    polyvinyl alcohol, and polyaminoacrylates.

19           31.    A device according to claim 30 wherein the water absorbing  
20    polymer is polyvinyl pyrrolidone.

21           32.    A device according to claim 30 wherein the silicone adhesive is  
22    a polysiloxane adhesive.

23           33.    A device according to claim 28 wherein the agent is selected  
24    from the group consisting of testosterone, progesterone, nandrolone, and  
25    estradiol.

26           34.    A device according to claim 33 wherein the agent is  
27    testosterone.

28           35.    A device according to claim 34 wherein the reservoir matrix  
29    comprises testosterone at or above saturation.

1           36.    A device according to claim 28 comprising 60-90% polysiloxane  
2    adhesive, 5-25% polyvinyl pyrrolidone, 1-15% testosterone, 1-20% glycerol  
3    monolaurate, and 1-20% lauryl acetate.

4           37.    A device according to claim 28 wherein the lauryl acetate is at  
5    least 97% pure.

6           38.    A method for the transdermal administration of an agent at a  
7    therapeutically effective rate comprising simultaneously coadministering to a  
8    body surface or membrane an agent and a permeation enhancing amount of  
9    a permeation enhancer mixture comprising lauryl acetate and a  
10   monoglyceride.

11          39.    A method according to claim 38 wherein the monoglyceride is  
12   glycerol monolaurate.

13          40.    A method according to claim 38 wherein the lauryl acetate is at  
14   least 97% pure.

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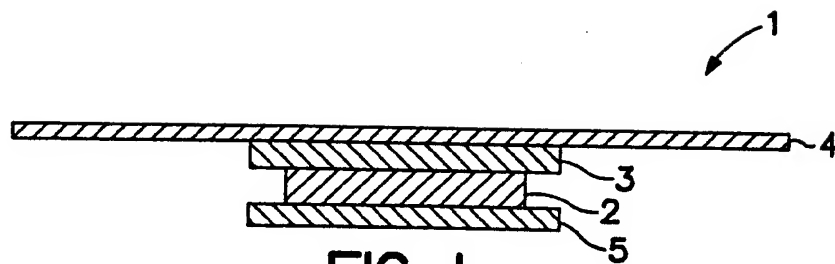


FIG. 1

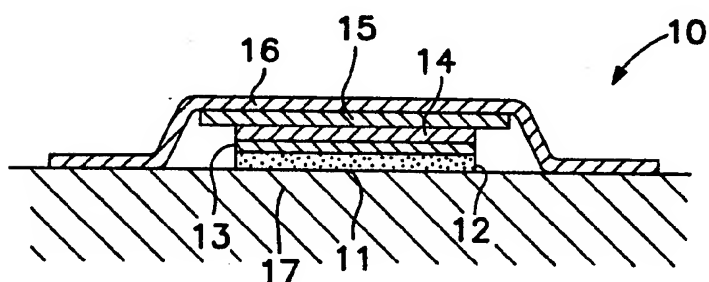


FIG. 2

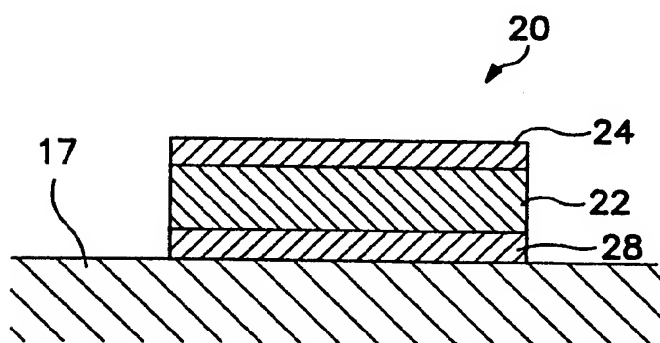


FIG. 3

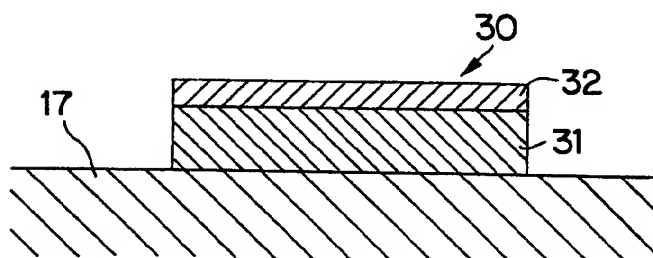
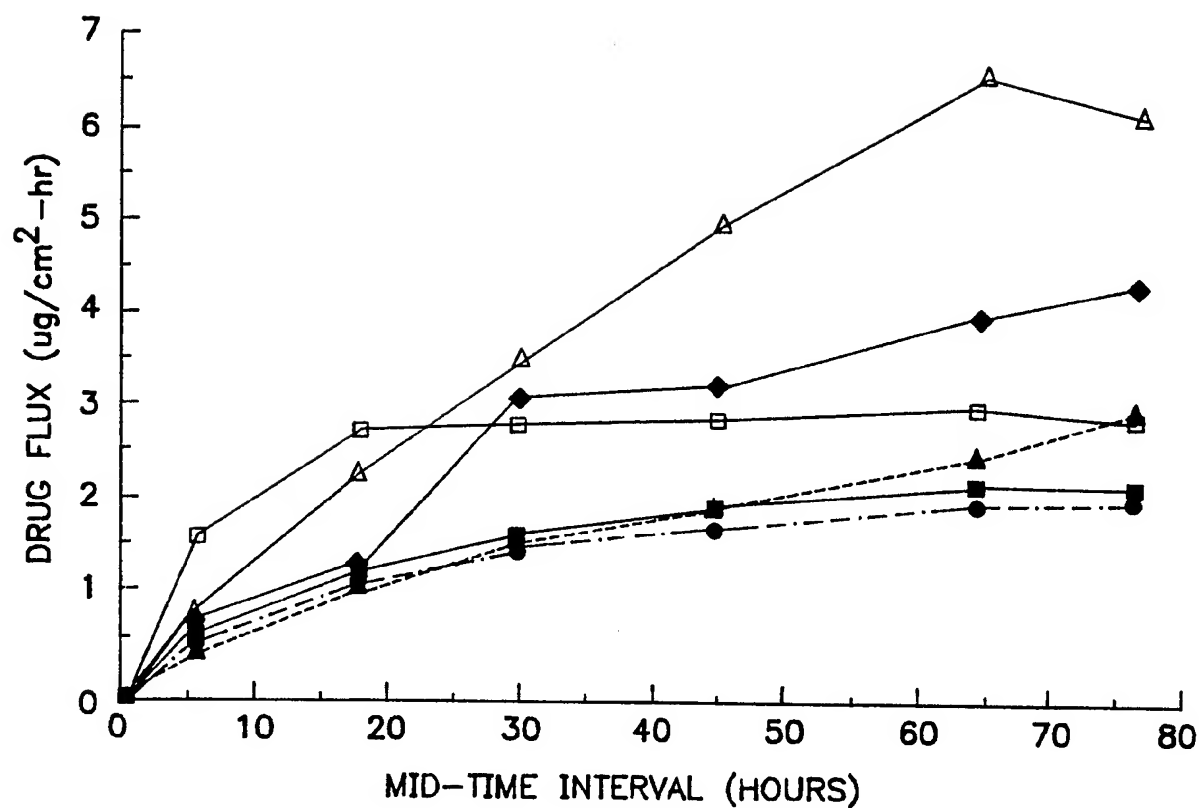


FIG. 4

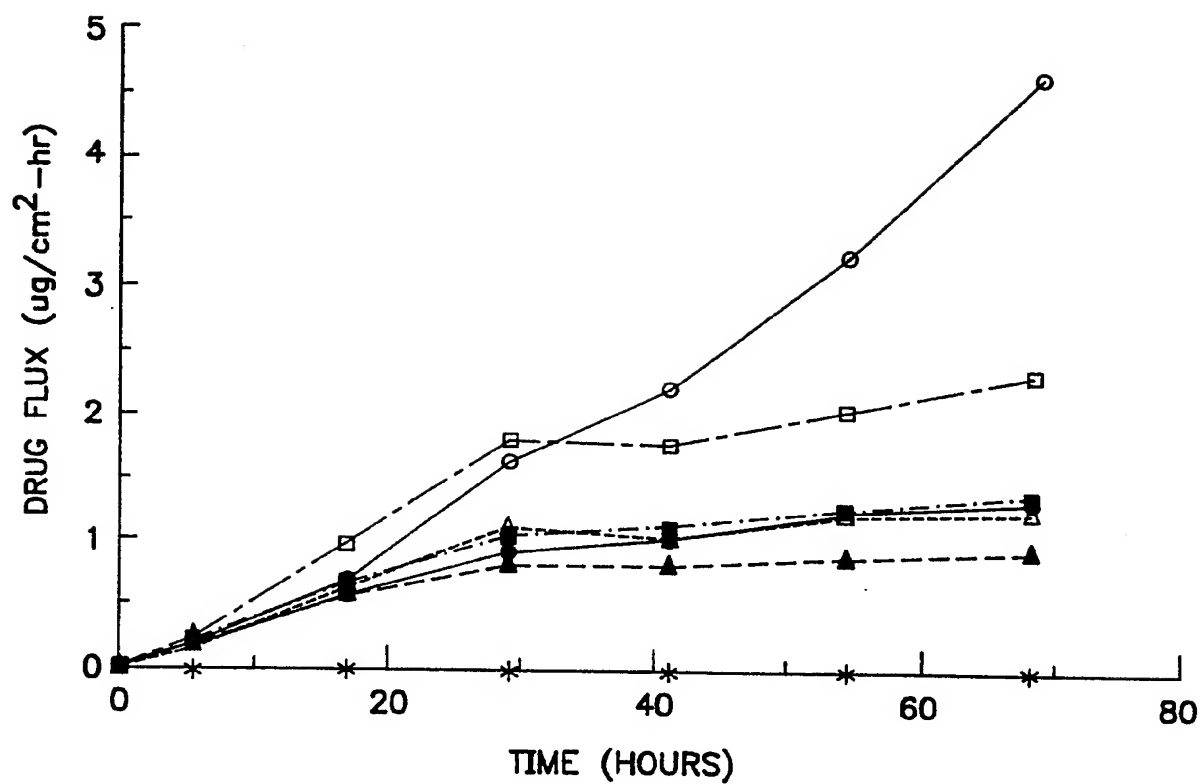
2 / 6



- △— APZ/GML/LA/EVA-40  
15/20/12/53
- ◆— APZ/GML/LL/EVA-40  
15/20/12/53
- APZ/GML/LL/EVA-40  
15/13/27/45
- ▲--- APZ/GMO/EVA-40  
15/30/55
- APZ/GMO/LL/EVA-40  
15/20/12/53
- APZ/GMO/ML/EVA-40  
15/20/12/53

FIG. 5

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- ALP/GML/LA/EVA40  
15/20/12/53
- △— ALP/GML/LA/EVA40  
15/13/27/45
- ALP/GML/LA/EVA40  
15/15/25/45
- ALP/GML/LL/EVA40  
15/20/12/53
- ▲-- ALP/GML/LL/EVA40  
15/13/27/45
- ALP/GML/LL/EVA40  
15/15/25/45
- \*— ALP/GML/LL/EVA40  
15/0/0/85

FIG. 6

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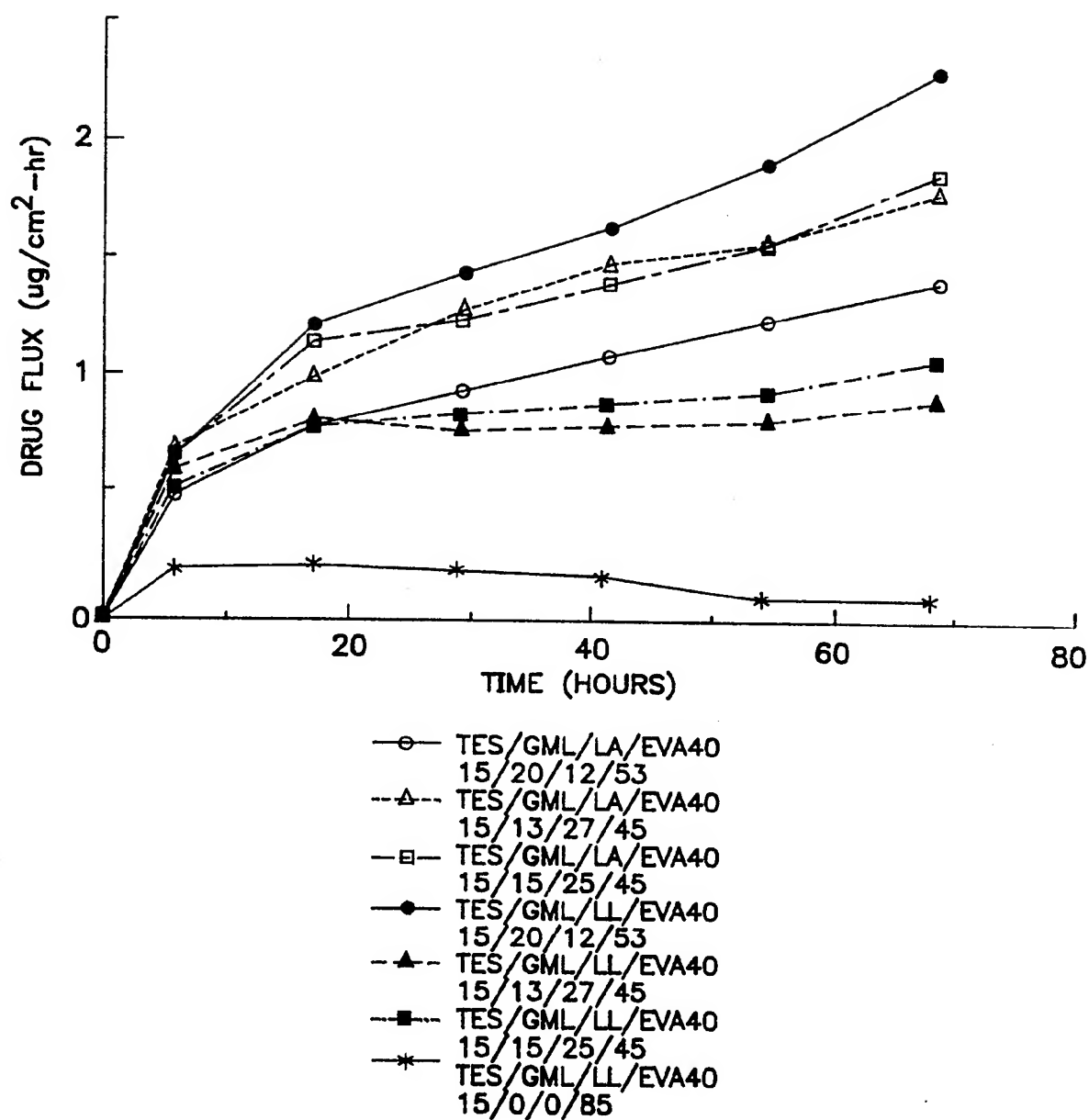


FIG. 7

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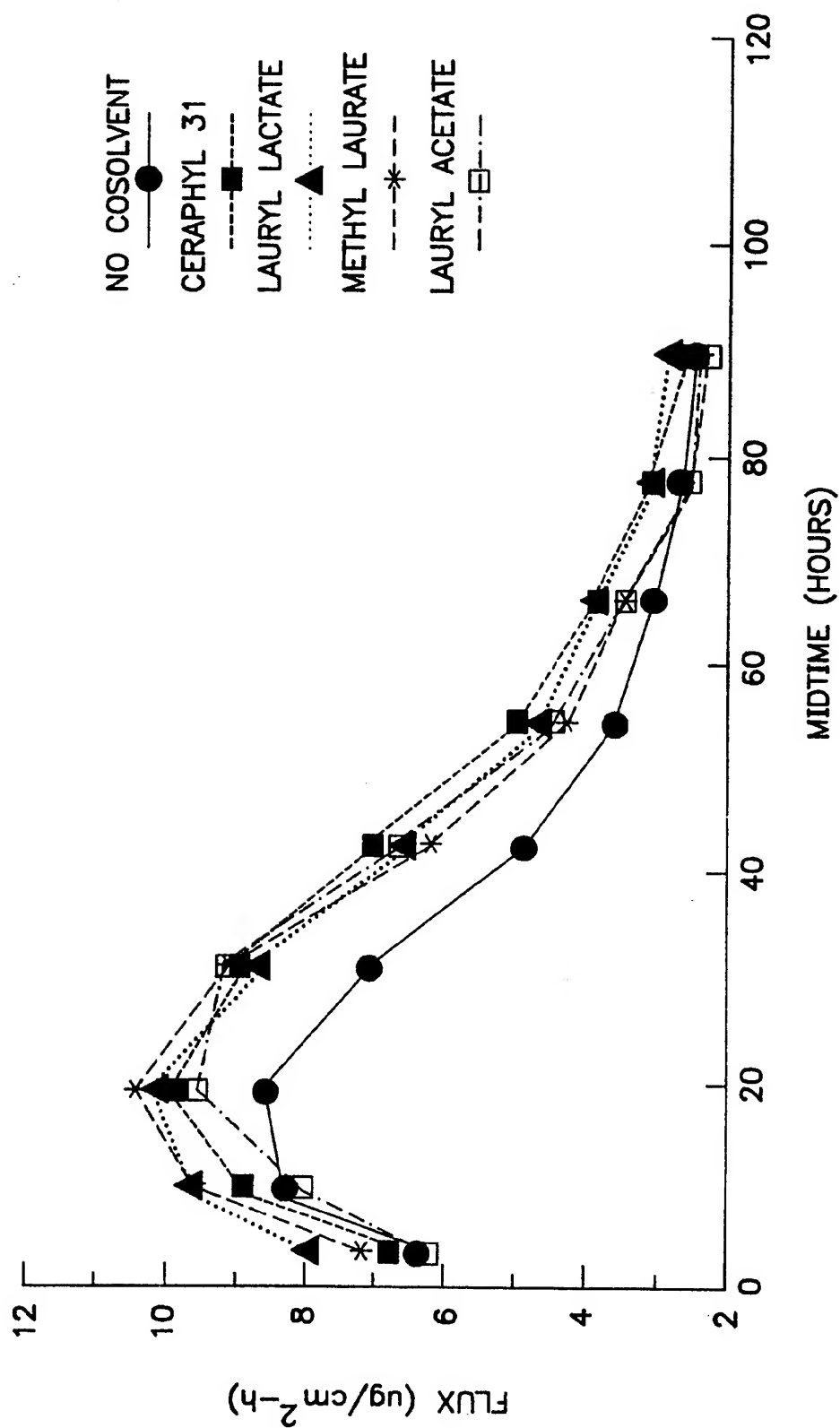


FIG. 8



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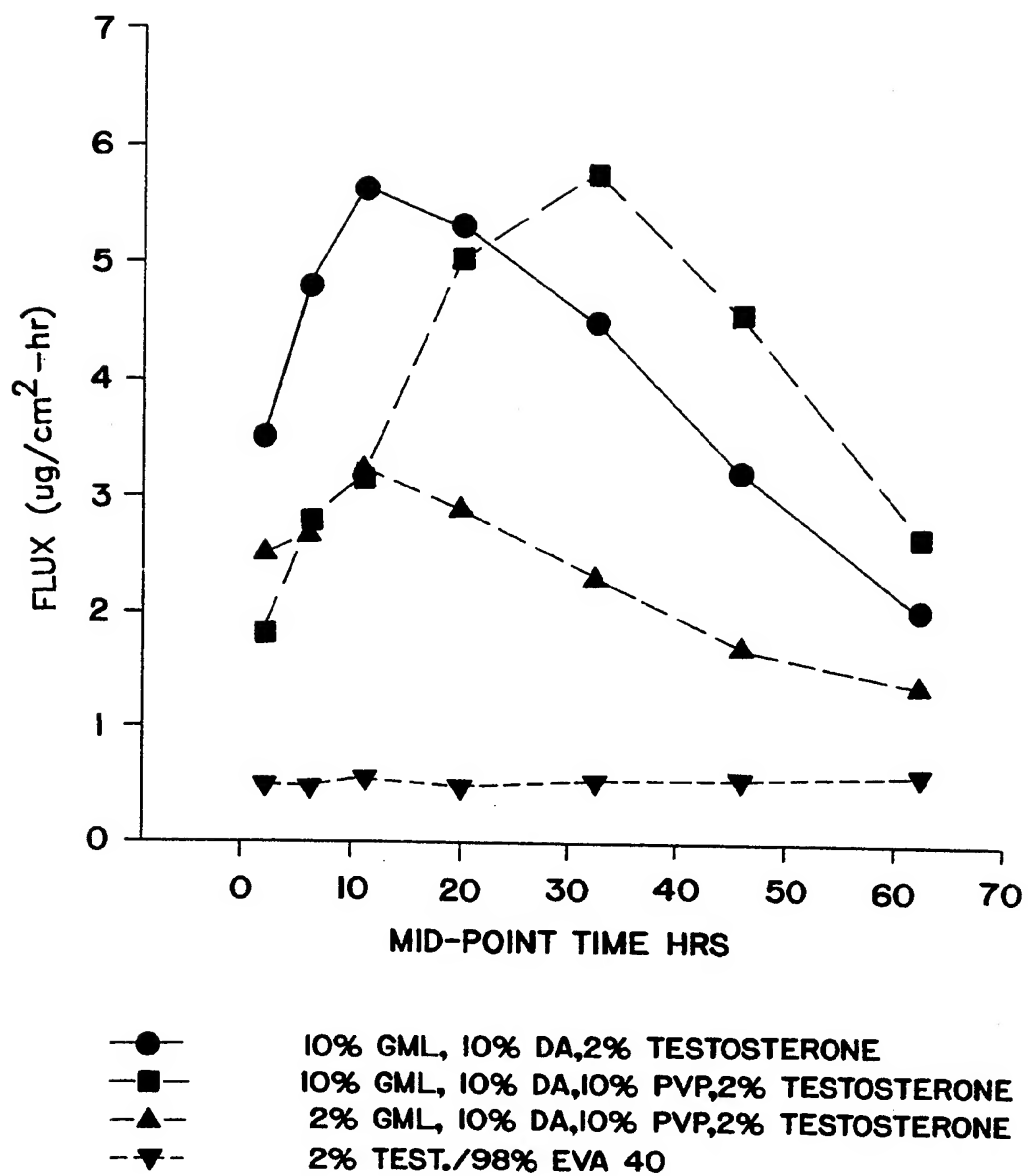


FIG. 9